

Complications of transrectal ultrasound-guided 12-core prostate biopsy: a single center experience with 2049 patients

Ozan Efesoy¹, Murat Bozlu², Selahittin Çayan², Erdem Akbay²

ABSTRACT

Objective: Currently, transrectal ultrasound-guided (TRUS) systematic prostate biopsy is the standard procedure in the diagnosis of prostate cancer. Although TRUS-guided prostate biopsy is a safe method, it is an invasive procedure that is not free from complications. In this prospective study we evaluated the complications of a TRUS-guided 12-core prostate biopsy.

Material and methods: The study included 2049 patients undergoing transrectal ultrasound-guided 12-core prostate biopsy used in the diagnosis of prostate cancer. The indications for the prostate biopsy were abnormal digital rectal examination findings and/or an elevated serum total prostate specific antigen (PSA) level (greater than 4 ng/mL). The participants received prophylactic oral ciprofloxacin (500 mg) the night before and the morning of the biopsy, followed by 500 mg orally twice daily for 2 days. To prevent development of voiding disorders, the patients also received oral alpha blockers for 30 days starting the day before the procedure. A Fleet enema was self-administered the night before the procedure for rectal cleansing. The complications were assessed both 10 days and 1 month after the biopsy.

Results: The mean age, serum total PSA level and prostate volume of the patients were 65.4±9.6 years, 18.6±22.4 ng/mL and 51.3±22.4 cc, respectively. From these 2.042 biopsies, 596 cases (29.1%) were histopathologically diagnosed as prostate adenocarcinoma. Minor complications, such as hematuria (66.3%), hematospermia (38.8%), rectal bleeding (28.4%), mild to moderate degrees of vasovagal episodes (7.7%), and genitourinary tract infection (6.1%) were noted frequently. Major complications were rare and included urosepsis (0.5%), rectal bleeding requiring intervention (0.3%), acute urinary retention (0.3%), hematuria necessitating transfusion (0.05%), Fournier's gangrene (0.05%), and myocardial infarction (0.05%).

Conclusion: TRUS-guided prostate biopsy is safe for diagnosing prostate cancer with few major but frequent minor complications. However, patients should be informed and followed-up after biopsy regarding possible complications.

Key words: Biopsy; complications; prostate; transrectal ultrasound.

¹Clinic of Urology, Develi Hatice-Muammer Kocatürk State Hospital, Kayseri, Turkey

²Department of Urology, Faculty of Medicine, Mersin University, Mersin, Turkey

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Correspondence:
Ozan Efesoy
Clinic of Urology, Develi Hatice-Muammer Kocatürk State Hospital, Kayseri, Turkey
Phone: +90 505 746 24 94
E-mail: oefesoy@yahoo.com

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Introduction

According to general statistics prostate cancer is the most frequently seen type of cancer, and cause of mortality after pulmonary/brnchial cancer.^[1] In our country, based on 2008 data of the Turkish Directorate of the Department of Fight Against Cancer, prostate cancer is the most frequently seen type of cancer with an incidence rate of 36.3/100.000 after trachea, lung, and bronchial cancers.^[2] Transrectal ultrasound-guided (TRUS) systematic prostate biopsy is accepted as the gold standard to establish the histopathological diagnosis of prostate cancer.^[3]

In 1989, Hodge et al.^[4] described TRUS-guided systematic 6 core (sextant) prostate biopsy. They also revealed inadequacy of biopsies targeted at areas of clinical suspicion, and demonstrated that systematic biopsies significantly increase diagnostic sensitivity of the detection of prostate cancer. With the introduction of systemic biopsy era, important changes, and developments have been made within years in the preparation of the patient for the biopsy. Thanks to these advances, TRUS-guided prostate biopsy can be easily applied under conditions of outpatient clinics with very few, and more tolerable serious unwanted side effects.^[3] Even though, serious complication rates are

much lower, minor complications are more frequently seen.^[5] In the present study, we aimed to evaluate complications seen in the patients who underwent TRUS-guided 12-core prostate biopsy in our clinic in the light of the current literature.

Material and methods

A total of 2049 cases who firstly underwent TRUS-guided prostate biopsies between January 2003, and December 2011 in Mersin University Faculty of Medicine Department of Urology because prostate examinations, and biochemical analyses revealed deformities as asymmetry, and hard nodules, increased (>4 ng/mL) serum total prostate-specific antigen (PSA) values and/or abnormal PSA derivatives were included in the study.

Preparation for the biopsy

Patients who received anticoagulant therapy were consulted to relevant disciplines, and acetylsalicylic acid, anticoagulants (low-molecular weight heparin, and warfarin) were discontinued 7, and 3 days before biopsy, respectively. Excluding patients requiring intervention because of development of bleeding episodes, anticoagulant therapy was reinitiated on the postprocedural first day. In all cases, before biopsy as antibiotic prophylaxis 500 mg ciprofloxacin was given twice daily for 2 days. To prevent voiding dysfunction, the night before the biopsy alpha-blocker therapy was initiated, and continued further for 30 days. For rectal cleansing the night before the biopsy patients used rectal enemas. All cases were informed in detail about the procedure, and their written informed consent forms were obtained.

Biopsy Technique

Following evaluation of the prostatic anatomy while the patient in the left lateral decubitus position, and periprostatic nerve blockade performed using 10 mL 2% lidocaine, 12-core biopsy specimens were obtained from the base of the right, and left prostate lobes, lateral, and far remote lateral to the midline, medial, and lateral parts of the apex. All of these procedures were performed under the guidance of standard gray-scale ultrasound, and 7.5 MHz rectal probe (Siemens Sonoline Adara, Erlangen, Germany) using 18 Gauge biopsy needle (Angiotech Tru-Core I, Florida, USA), and automatic biopsy gun (Angiotech Tru-Core I, Florida, USA). Distal ends of all biopsy specimens were marked with an ink, and sent to the pathology laboratory in individually numbered tubes.

Post-biopsy evaluation

The patients were observed for nearly half an hour after biopsy, and informed about potential complications, and emergencies which require referral to the hospital, before they were discharged. The patients were evaluated as for the complications of biopsy, on 10. day after the biopsy, and on 30. day when histopathological examination results were obtained.

Statistical analysis

Data were statistically analyzed using Statistical Package for the Social Sciences version 11.5.2.1 (SPSS Inc, Chicago, USA). As descriptive statistics for continuous variables mean \pm standard deviation, and for categorical variables rates, and percentages were used.

Results

Mean age of the cases [65.4 \pm 9.6 years (42-79 yrs)], mean serum total [18.6 \pm 22.4 ng/mL (2.5-200 ng/mL)], and free [4.5 \pm 10.7 ng/mL (0.8-29)] PSA concentrations, and mean prostate volumes [51.3 \pm 22.4 cc (23-130 cc)] were also determined. Histopathological diagnosis of 596 (29.1%) cases was prostate adenocarcinoma.

In 1623 (79.2%) cases minor complications as macroscopic hematuria, hematospermia, rectal bleeding, vasovagal symptoms, genitourinary system infection, fever, persistent dysuria, and in 27 (1.3%) cases serious complications as urosepsis, transfusion requiring hematuria, Fournier's gangrene, and myocardial infarction were detected. Observed complications, and their frequencies are summarized in Table 1.

Macroscopic hematuria was observed in 1358 (66.3%) cases and lasted an average of 2.8 (1-18 days) days. Hematuria was seen 1 (37.8% of the cases), 2 (23.8%), 6-10 (11.9%), and >10 (0.7%) days after biopsy procedure. Only in one case (0.05%) transfusion requiring hematuria developed. Hematospermia (n=795; 38.8%), and rectal bleeding (n=581; 28.4%) were also seen. Rectal bleeding lasted for an average of 1.6 days (1-12 days), and it was observed 1 (59.9% of the cases), 2 (31.5%), 3-5 (7.2%), 6-10 (1.2%), and >10 days (0.2%) after biopsy procedure. Rectal bleeding requiring intervention developed in 6 (0.3%) cases. In 5 of these cases balloon of the Foley catheter was inflated up to 50 cc, and bleeding points were compressed to achieve hemostatic control, while one case required colonoscopy, and endoscopic sclerotherapy.

Suggestively, biopsy-related signs of infection (fever, dysuria, and leukocytosis etc.) were detected in 348 (16.9%) patients, while in 96 (4.7%) patients only fever was observed. In 137 (39.4%) cases culture positivity was observed. *Escherichia coli* (78.1%), *Enterococcus spp.* (9.5%), *Enterobacter spp.* (7.3%), *Pseudomonas spp.* (2.2%), *Klebsiella spp.* (2.2%), and *ve MRSA* (0.7%) were isolated from bacterial cultures. Infectious complications included simple genitourinary system infection which regressed with antibiotherapy (n=125; 6.1%), urosepsis (n=11; 0.5 %), and Fournier's gangrene (n=1; 0.05%).

In 158 (7.7%) cases vasovagal symptoms as sweating, nausea, paleness, dizziness, and hypotension were observed. In all

Table 1. Complications, and their frequencies detected in our series

Minor	n/N	%	Serious	n/N	%
Macroscopic hematuria	1358/2049	66.3	Urosepsis	11/2049	0.5
Hemospermia	795/2049	38.8	Rectal bleeding requiring intervention	6/2049	0.3
Rectal bleeding	581/2049	28.4	Acute urinary retention	7/2049	0.3
Vasovagal symptoms	158/2049	7.7	Hematuria requiring transfusion	1/2049	0.05
Genitourinary system infection	125/2049	6.1	Fournier's gangrene	1/2049	0.05
Fever	96/2049	4.7	Myocardial infarction	1/2049	0.05
Persistent dysuria	68/2049	3.3			
Dysuria	23/2049	1.1			

patients, these symptoms regressed when the patient was laid in the Trendelenburg position. However in one (0.05%) case, angina pectoris developed just after the biopsy. The patient was consulted to the Department of Cardiology. Upon detection of inferior myocardial infarction, the patient was treated with percutaneous transluminal coronary angioplasty, and discharged on the postoperative 5 day. In these patients persistent dysuria (n=68; 3.3%), voiding disorders (n=23; 1.1%), and acute urinary retention (n=7; 0.3%) were detected.

Discussion

In our era, prostate biopsies have been performed more frequently because of widespread use of PSA test in the diagnosis of prostate cancer, increasing awareness of the community about prostate cancer, prevalent use of early diagnosis, and treatment programs, and gradually increasing number of aging population in the world.^[6]

Despite superiorities of TRUS-guided prostate biopsy, its invasive characteristics, and rectal application result in the development of some potential complications. Indeed, in the first publications which evaluated outcomes of prostate biopsies, higher serious complication rates predominantly infections, and procedure-related mortalities were reported.^[7] As years go by, important advancements related to biopsy technique, antibiotic prophylaxis, use of automatic biopsy gun, and pre-biopsy preparation have been achieved which led to decrease in serious, and complex complication rates, while minor complication rates are still at a considerable level.^[5,7] In the multicentered European Prostate Cancer Screening Study, Djavan et al.^[5] performed 8-core TRUS-guided prostate biopsy on 1051 men, and reported minor, and serious complication rates as 69.7, and 0.01, respectively. In our series, minor, and serious complication rates were detected as 79.2, and 1.3%, respectively. Complication rates of TRUS-guided prostate biopsies in several literature studies are presented in Table 2.

Bleeding episodes take the lead among TRUS-guided prostate biopsies. Bleeding episodes can emerge as hematuria, hemospermia, and rectal bleeding, and it can be seen in a wide spectrum ranging from minor bleeding to life-threatening disseminated intravascular coagulopathy.^[8]

Hematuria is the most frequently seen complication following TRUS-guided prostate biopsy. Hematuria with an incidence ranging between 14.4, and 84%, persists for an average of 2.7-5.1 days which can extend up to 20 days.^[5,7,9-21] As a minor complication, hematuria which is frequently encountered after biopsy, generally lasts briefly without any need for additional treatment. However, in 0.25-0.7% of the cases hematuria leading to clot retention and/or requiring transfusion can be seen.^[5,13] Hemospermia which is another frequently seen complication has been reported in 5.7, and 89% of the cases.^[5,7,9,10,12-19,21] Though hemospermia does not generally require additional treatment, it might trigger serious concerns in previously unwarned patients. Hemospermia lasts an average of 10.9 days, however it might occasionally persist up to 10.9 days.^[6,17] Rectal bleeding has been reported in 1.3, and 39.6% of the cases.^[5,7,9-12,14-21] Generally rectal bleeding lasts for 1-5 days, and resolves spontaneously, however in some cases it might persist up to 15 days.^[6,17,21] However in 0.01-2.1% of the cases, rectal bleeding requiring intervention can be seen.^[5,7,12,18,19,21] In the presence of marked rectal bleeding leading to hemodynamic impairment, intrarectal compression is applied on rectal bleeding points by finger, ultrasound probe or anoscope to achieve hemostasis or placement of an intrarectal tampon can achieve hemostatic control in most of the cases. If these methods fail, colonoscopic, and endoscopic sclerotherapy might be required.^[8] In our series, hematuria, hemospermia, and rectal bleeding seen as minor complications were detected in 66.3, 38.8, and 28.4%, of the cases, respectively. However transfusion requiring hematuria, and rectal bleeding necessitating bleeding were detected in 0.05, and 0.3% of the cases, respectively.

Table 2. Complication of TRUS-guided prostate biopsies: literature data

Author	Cases (n)	Cores (n)	%					
			Hematuria*	Hemospermia*	Rectal bleeding*	Fever	AUR	Hospitalization
Djavan et al. ^[5]	1051	8	62	9.8	2.1	2.9	0.9	2.9
Çam et al. ^[7]	281	8	19.5	30.9	5.3	2.8		1.42
Hammerer&Huland ^[9]	651	6	14.4	5.7	2.3			
Rietbergen et al. ^[10]	1687	6	23.6	45.3	1.7	4.2	0.4	0.4
Enlund&Varenhorst ^[11]	415	6	49.6		21.7	2.9	0.2	0.7
Rodriguez&Terris ^[12]	128	6	84	9.1	9.9	1.7	1.6	0.8
Önder et al. ^[13]	858	6	43	17.9				1.2
Deliveliotis et al. ^[14]	120	6	65	29.1	33.3	6.6	4.6	1.7
Naughton et al. ^[15]		6	49	71	10			
	160	12	60	89	24			
Raaijmakers et al. ^[16]	5802	6	22.6	50.4	1.3	3.5	0.4	0.5
Peyromaure et al. ^[17]	289	10	74.4	78.3	39.6	3.7		
Avcı et al. ^[18]	1270	12	21	29	18		0.7	
Berger et al. ^[19]	5957	6,10,15	14.5	36.3	2.3	0.8	0.2	
Paul et al. ^[20]		6	57.6		18.3	2.4		
	405	10	72		29.3	2.2		
Ghani et al. ^[21]	307	6	44	13	17			
	325	8	41	16	26			
	128	12	39	12	27			

*Bleeding not requiring intervention

Development of infectious complications ranging from asymptomatic bacteriuria to septic shock is probable through manipulation of the infected prostate tissue during TRUS-guided prostate biopsy or transport, and implantation of rectal flora bacteria into prostate tissue, urine, and blood via biopsy needle. Most of the serious complications related to TRUS-guided prostate biopsies are associated with infections.^[6] Lack of any standardized definition of infectious complications, differences in biopsy technique, and pre-biopsy preparations complicate determination of incidence of these complications.^[6,8] Post-biopsy infectious complications are mostly caused by *Escherichia coli*, *Enterococcus* and *Enterobacter spp.*^[12] In the literature, diverse definitions, and incidence rates of infectious complications have been reported in various studies which used different biopsy techniques, and patient preparation. the literature.^[5,7,10-14,16-20] Another uncertainty concerning infectious complications relates to the impact of pre-biopsy rectal cleansing on infectious complications. Whereas various authors have reported that enema used for rectal cleansing before biopsy decreased, did not change or even increase infectious complication rates.^[8] Even contrary opinions were asserted in some

publications, necessity of prophylactic antibiotic use has been revealed in prospective, randomized, controlled studies.^[11,22] In a current article, Puig et al.^[22] used antibiotic prophylaxis in 614 cases in a series of 1018 patients whom they performed TRUS-guided antibiotic prophylaxis, while 404 patients did not receive antibiotic prophylaxis. Infectious complication rates in groups who received or didn't receive prophylactic post-biopsy antibiotherapy were 3.7 vs. 10.3%, respectively (p=0.0001). While the authors reported that serious infectious complications were seen at a lower incidence (24%) in the prophylaxis group when compared with the untreated patients (75.6%) (p=0.0410).^[22] Although a consensus has been almost reached about requirement of preprocedural antibiotic prophylaxis, uncertainty exist concerning choice of appropriate antibiotics, and duration of prophylactic antibiotherapy.^[6]

Other complications frequently seen related to TRUS-guided prostate biopsy are vasovagal symptoms, and voiding dysfunction. Vasovagal symptoms which can be seen during, and immediately after biopsy are thought to be the result of vasodilation of gastrointestinal system vasculature or pooling of blood within

the gastrointestinal system as a reflexive response to distention of rectal wall vessels which decrease the amount of blood delivered into brain, and hence cerebral hypoperfusion.^[8] In most of the cases, overall incidence of vasovagal symptoms triggered by anxiety, and hypoglycemia, and moderate to severe symptoms has been reported to range between 1, and 8%, and 1.2, and 5%, respectively.^[5,12,13,23] Some measures should be taken which include informing the patients about the procedure to alleviate their anxiety, and, recommending them to undergo biopsy on a full stomach in order to prevent development of hypoglycemia. Besides the patient should not be ambulated immediately after the procedure. They should rest firstly in supine position, and then sit erect for a while to avoid emergence of vasovagal symptoms.^[23] Despite all of these precautions, if vasovagal symptoms are still observed, then placing the patient in Trendelenburg position is usually suffice. Since in some cases IV fluid infusion can be required, equipments for intravenous access, IV replacement fluid, and emergency intervention set should be at hand in the biopsy room.^[8] In our series, in 158 (7.7%) cases vasovagal symptoms which regressed with Trendelenburg position, and did not require additional intervention, in one case (0.05%) immediately after the procedure angina pectoris, and inferior myocardial infarction developed.

The association between prostate symptom scores before biopsy, and trauma, edema, and voiding disorders due to the clots formed after bleeding has been demonstrated in various studies.^[12,24] In many series persistent dysuria (7-7.2%), voiding disorders (0.8-40%), and acute urinary retention (AUR) (0.2-9.1%) have been reported in various incidence rates.^[5,10-12,14,16,18,19,24,25] In their prospective study, Bozlu ve et al.^[24] performed TRUS-guided 12-core prostate biopsies on 66 patients, and randomized them in control, and alpha-blocker (tamsulosin) groups. They found that development of AUR, and voiding difficulties which started at 7. postprocedural day were lower in the tamsulosin group relative to the control group (3 vs. 9.1%, and 9.1 vs. 42.4%, respectively). Efesoy et al.^[25] compared effects of four different alpha-blockers (alfuzosin, doxazosin, tamsulosin, and terazosin) on post-biopsy voiding disorders, and found that development of AUR, and voiding disorders which become manifest from 7. postprocedural day on were less frequently seen in the alpha-blocker group when compared with the control group. (1.25 vs. 7.5%, and 6.9% vs. 42.5%). The authors also pointed out to the non-superiority of these alpha-blockers with respect to these favorable effects. In this series where we routinely started alpha-blocker therapy, and in comparison with untreated series, we detected very low rates of persistent dysuria (3.3%), voiding disorder (1.1%), and AUR (0.3%). Based on available data it seems to be a reasonable approach to give prophylactic alpha-blocker therapy targeted at post-biopsy complications which might develop in the future.

In conclusion, TRUS-guided prostate biopsy is a tolerable procedure by the patients which can be easily applied on an ambulatory basis. Thanks to the developments in the preparation of the patient before the biopsy, and biopsy techniques, rates of serious, and complex complications have decreased considerably, while rates of minor complications are still at higher levels. Since antibiotic prophylaxis has decreased infectious complications, antibiotherapy should be instituted for a short-term in patients without any risk factor. However high-risk patients should receive long-term antibiotic prophylaxis. When gradually increasing bacterial resistance to ciprofloxacin in our country taken into consideration, regional, and nationwide questionnaire surveys should be performed to determine ideal prophylactic antibiotherapy. Measures to decrease complications seen during, and after biopsy include informing patients about the procedure in order to decrease their levels of anxiety, avoidance of hypoglycemia during the procedure, use of anesthetic techniques to prevent painful episodes, and alpha-blockers for the prophylaxis against voiding disorders.

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